REMARKS

1. Amendments to the Claims

Claims 1-5, 7-10, 12-15, 17-22, 25-27, 29, 32, 34-43, and 46-48 were previously examined. Claim 27 is herein canceled. Claims 50-52 are herein added.

Claim 48 is herein amended. Support for claim 48 is found in the Specification at page 13, lines 26-29. Claims 46 and 47 are herein canceled and re-added as new claim 50, which is dependent on claim 48.

Claim 51 is added. Support for claim 51 is found in the Specification at page 9, lines 35-38. Claim 52 is supported by cancelled claims 46 and 47.

No new matter has been added.

2. Novelty

The Examiner maintains the rejection of claims 1-5, 7-8, 10, 12-15, 18-19, 22, 46, 48, and 49 under 35 U.S.C. § 102(b) as being anticipated by U.S. Patent No. 5,716,595 (hereinafter Goldenberg et al.). Applicants note that claim 46 was only rejected as being anticipated by Goldenberg et al. The Examiner maintains the rejection of claims 1-5, 7-8, 10, 12-15, 18-19, 48, and 49, under 35 U.S.C. § 102 (b) as being anticipated by U.S. Patent No. 6,107,102 (Ferrari). Applicants respectfully traverse.

Applicants submit that Goldenberg et al. and Ferrari do not anticipate the present invention because the antibodies of Goldenberg et al. and Ferrari are not native antibodies having ADCC and CDC effector functions.

Ferrari does not disclose a native antibody because the antibodies of which the Examiner speaks (discussed in col. 12, lines 49-52, and col. 15, lines 45-63) are not directed to the tumor, but are directed to a LDL or a viral antigen. Such antibodies as described by Ferrari are directed against

the tumor antigens and are modified e.g. by immobilization on a "microdevice" and therefore, are not "native" antibodies.

Moreover, with regard to claim 48, such antibodies do not "consist of" two heavy chains and two light chains, they also include the attachment to the microdevice.

Goldenberg et al. also do not disclose using therapeutically active antibodies, in fact monovalent antibody fragments are used (claim 1). These antibody fragments are discussed on col. 12, lines 33-52 and only relate to such antibody fragment without a Fc portion. However, according to the present invention, an unmodified Fc portion is necessary to be a native antibody and to have the required ADCC or CDC function.

Moreover, with regard to claim 48, the antibodies of Goldenberg et al. do not "consist of" two heavy chains and two light chains, and they also include the label. The Specification indicates that labeled antibodies are to be avoided on page 9, lines 36 and 37.

Thus, Applicants submit that neither Goldenberg et al. nor Ferrari anticipate the claimed invention.

3. Obviousness

The obviousness rejections are based on either Goldenberg et al. or Ferrari in combination with some arrangement of Schlimok et al., Crisan, and U.S. Patent No. 5,792,456 ('456). Specifically, the Examiner rejects claims 1, 9, 17, 20, 25-27, 29-32, 35-40, 43, and 47 as being unpatentable over Goldenberg et al. in view of Schlimok et al. and Crisan et al. The Examiner rejects claims 21, 34, 41 and 42 as being unpatentable over Goldenberg et al., Schlimok et al., Crisan et al., and further in view of U.S. Patent No. 5,792,456 (Yelton). The Examiner rejects claims 1, 9, 17, 20, 25-27, 29-32, 35-40, 43, and 47 as being unpatentable over Ferrari in view of Schlimok et al. and Crisan. The Examiner rejects claims 21, 34, 41, and 42 as being unpatentable over Ferrari, Schlimok et al., Crisan, and further in view of Yelton.

According to the Examiner, a possible reduced efficiency due to the labeling of the antibodies or antibody fragments of Goldenberg et al. is not necessarily sufficient to discourage the skilled man in the art from a combination of these references with Crisan et al. and Schlimok et al.

The Examiner explains (on p. 8, 3rd paragraph of the present Office Action) that motivation for combining these documents is shown in Schlimok et al. which shows that Lewis Y antibodies can bind disseminated tumor cells and Crisan et al. show that during a surgical intervention disseminated tumor cells are increased. Thus, the Examiner concludes it is obvious to use Lewis Y antibodies in order to remove disseminated tumor cells during a surgical intervention.

Applicants respectfully disagree with this assessment, and submit that one of skill in the art, reading Schlimok et al., would have no reasonable expectation of success based on the failed therapies presented therein (see below).

a. Goldenberg et al. and Schlimok et al. in combination with the other references do not disclose every element of the claimed invention.

As a preliminary matter, Applicants maintain that Goldenberg et al. and Schlimok et al. in combination with the other references do not teach, with a reasonable expectation of success, the inhibition of the dissemination of tumor cells. In addition, as discussed above, Goldenberg et al. do not teach a native antibody. Also, Applicants submit that Schlimok et al. may have disclosed a CDC effect, but is completely silent about ADCC effects. But, the ADCC effector function is required by the claims. Thus, Schlimok et al., in combination with the other references fail to teach every element of the claimed invention. Applicants request that the rejection be withdrawn.

b. One of skill in the art would not have a reasonable expectation of success in performing and achieving the desired result of the claimed method based on the data presented in Schlimok et al.

Applicants submit that as Schlimok et al. disclose that the administration of a Lewis Y antibody is not effective to inhibit cancer cell dissemination, one of skill in the art would not have a reasonable expectation of success in achieving the claimed invention based on this reference.

Schlimok et al. disclose a monoclonal antibody mAb ABL 364 produced by the mouse hybridoma cell line BR55-2. In the past the Examiner has stated that Tables 3 and 4 of Schlimok et al., demonstrate that disseminated tumor cells can be reduced.

However, these results actually demonstrate that, in several patients, the Lewis Y antibody as used according to the methods of Schlimok et al. is not effective. Indeed, Schlimok et al. disclosed that the mouse antibody ABL 364 was tested in 40 patients (abstract and p. 1800, 2nd paragraph). In 30 of these patients the proposed therapy did not result in a reduction of CK-positive cells (abstract, 3rd sentence). Only 10 breast cancer patients were further investigated. The results of these 30 breast cancer patients are shown in Table 3 and Table 4 on p. 1802. Referring to Table 3, the text portion on p. 1801, right column, 2nd paragraph, mentions that "as to the clinical manifests metastasis (Table 3), no objective regression of the metastatic lesions could be ascertained by conventional diagnostic techniques, such as [...]". Furthermore, the article expressly indicates that the therapy was not effective "[w]ith the exception of a few anecdotal and transient remissions, no consistent survival benefit occurred for treated pateints." (Schlimok, 1802, right column, paragraph 1). Clearly, the antibodies did not provide any useful results on these metastatic tumors.

By looking further at the details of Tables 3 and 4 it is apparent that from the 10 patients shown (which is only a subgroup of the initially investigated 40 patients) that some patients have an erratic tumor cell count progression with lowered cell counts with or without treatment. For example, in the placebo phase patient 36 showed increased cell counts after therapy initiation. Likewise, patient 37 showed a gradually increased cell count. Even the patients which allegedly have 0 CK-positive cells after an alleged positive therapy (patient 30, table 4) still developed progressive lung metastasis followed by death after 10 weeks after therapy (patient 30 according to Table 3). In fact, only 3 patients had a 0 CK-positive cell count after a therapy according to Table 4 and one of them (patient 30) has not even been truly treated. Thus, 2 out of 40 patients showed a positive result. Clearly, such poor data, with unreliable and inconsistent cell count data, can hardly be considered a true therapeutic method by a skilled person in the art.

Furthermore, only CK-positive cells in bone marrow were investigated according to Table 4. However, the occurrence of CK-positive cells in bone marrow is not equivalent to the inventive prevention of dissemination during a surgical intervention. Thus, the disclosures of Schlimok et al. do not establish inhibition of dissemination of tumor cells. On the other hand, according to the present invention, the separation of tumor cells into the blood stream is prevented and also the tumor cells are targeted and killed through CDC and ADCC actions, among others (specification, p. 14, 4th paragraph).

The results of Tables 3 and 4 of Schlimok et al. therefore do not support the claimed therapy, and further conclusions based on Tables 3 and 4 are purely speculative. In fact, Schlimok et al. only proposed that monitoring micrometastasis in bone marrow "might" be feasible and further improvements will be required for adjuvant therapies (abstract, last sentence). Using the anti-Lewis Y antibody itself (relevant to claims 26 and 29, especially) is not proposed at all as a sufficient therapy and Schlimok et al. expressly teach away from such a course by suggesting that "unmodified murine antibodies lack the capacity to kill epithelial tumour cells." (Schlimok, 1802, right column, paragraph 1). Thus, Schlimok teaches away from the usage of native antibodies.

Therefore, it is not obvious to combine the teachings of Goldenberg et al. (which do not disclose any treatment at all) or Crisan et al. (which only mention that disseminated tumor cells might occur, but provide no solution to this problem) to arrive at an effective treatment method such as the present invention.

c. Other evidence supports the unexpectedness of the effects of the claimed inventive method.

Moreover, other evidence supports a showing that the activity of the anti-Lewis Y antibody of the present invention is unexpected (especially relevant to claims 26, 29 and claims dependent thereon). As shown in U.S. Patent No. 7,527,789, the Lewis Y antibodies inhibit cell signaling thereby inhibiting MAP kinase. This MAP kinase inhibition by binding to Lewis Y structures on EGFR lowers tumor cell viability and cell proliferation which, in addition to the ADCC and CDC activities, is a further previously unknown mode of action which surprisingly shows that the

inventive use of anti-Lewis Y antibodies is suitable to prevent tumor cell metastasis formation. For this additional reason, Applicants request that the rejection be withdrawn.

Applicants believe the pending application is in condition for allowance. Applicants earnestly request allowance of all of the claims.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact Leonard R. Svensson Reg. No. 30,330 at the telephone number of the undersigned below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37.C.F.R. §§1.16 or 1.17; particularly, extension of time fees.

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Respectfully submitted,

By _____

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